

FILLING IN SOME GAPS ABOUT WERNER SYNDROME

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Interest in the neoplasia of Werner syndrome (WS) was renewed in 1996 with the publication of a literature review that revealed 147 cancers, precursors of cancer or benign meningiomas in Japanese and 39 in non-Japanese. This report was a result of a small group meeting in 1994 under the U.S.-Japan Cooperative Cancer Research Program. Further details are presented here. Acral lentiginous melanoma (ALM), which has the same low incidence rates in all races, occurred on the feet of 13 Japanese with WS as compared with less than one case expected. The distribution by site of osteosarcomas was unusual: the ankle or foot was affected in 7 of 10 patients with osteosarcoma vs. one observed among 36 cases in the same age range (35–57 years) diagnosed at the Cancer Institute Hospital in Tokyo. This double aggregation (ALM and osteosarcoma) at the same site suggests an effect of weight-bearing on tissue made vulnerable by muscle-wasting, lack of subcutaneous tissue, scleroderma, osteoporosis, ulcers and gangrene. Now that the WS gene (*WRN*) has been cloned it is possible to identify mutational homozygotes among the offspring of WS patients. Screening can be an asset in the early management of WS-related disorders, and in prospective study of the natural history of WS. Steps can be taken to lessen morbidity by early detection and treatment of diabetes mellitus, hyperlipidemia and cancers, especially of the thyroid. Perhaps the use of cancer chemoprevention should be considered. Because the first sign of WS is absence of the adolescent growth spurt, high school health records could be used to select students who do not grow in this interval to be screened for WS in high-rate areas. Japan has the best opportunity in the world for making such a study because of the high prevalence of cases there.

The Role of the U.S.-Japan Cooperative Cancer Research Program

This program of the (U.S.) National Cancer Institute and the Japan Society for the Promotion of Science began in 1974 and ran for 22 years. Dr. Haruo Sugano and I were the coordinators for the Interdisciplinary Area, and organized or oversaw 31 small-group seminars on epidemiology, geographic pathology, genetics and biostatistics, 1981–1996 (9).

In February 1994 the topic was Cancer Clusters. As we were selecting participants, Dr. Sugano saw a note in a Tokyo medical newsletter that told of a rheumatologist, Dr. Makoto Goto, who had assembled a large series of case-reports of

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patients with Werner (premature aging) syndrome and rare cancers. Dr. Sugano invited Dr. Goto to speak at the Cancer Institute in Tokyo and then to Honolulu for the seminar on cancer clusters. Dr. Goto worked at a city hospital largely on his own, so Dr. Sugano, his staff member, Dr. Yuichi Ishikawa — a pathologist, and I helped assemble the data for presentation and interpretation.

Werner syndrome has become a prominent topic in Japan, where it is more common than elsewhere because of the influence of inbreeding on this autosomal recessive gene. The clinical information in Japan far exceeds that for all the rest of the world — 147 cancers in the Japanese group vs. 39 in Caucasians, according to the 1996 review of the literature (5). Dr. Goto has been a leader of these studies from the beginning. More than 50% of the neoplasms were non-epithelial (Monnat, chapter 10), as compared with 10% in the general population of the U.S. (10).

Excess of a Rare Melanoma Subtype

A rare form of melanoma occurs on the hands and feet and under the nails. It is not related to sun exposure as other melanomas are. It is known as acral lentiginous melanoma (ALM), and has the same frequency, about 1.6/million/year in Japanese as in Caucasians (3) and Blacks (21). The combined incidence rate of other melanoma subtypes has about the same incidence as ALM in Japanese (3), but is much higher in Caucasians. Thus the ratio of other melanoma to ALM is 100: 1 in Caucasians (11) and 1:1 in Japanese. Because 50% of melanomas are classified as ALM in Japanese, it is a common misconception that this is a high rate, when in fact it is due to a low rate of other melanomas.

At the rate of 1.6/million/year, less than one case of ALM would be expected among 2,000 patients with WS, the estimated number in Japan, 1917–1999 (19). Remarkably, 13 ALM of the foot have been found and 5 of the nasal mucosa (two of them in sisters) (5). Melanomas of nasal mucosa, which are extremely rare, add to the unique cluster of these neoplasms in WS. Study of unusual clusters of disease can provide clues to etiology, environmental when the people are not related to one another, (e.g., lung carcinoma in mustard-gas workers), and genetic when in families, e.g., retinoblastoma. The high rate of nasal melanomas in Japanese with WS strongly suggests an interaction between an as yet unidentified environmental carcinogen and a genetically susceptible host.

In addition to the excess of ALM there was also a cluster of osteosarcoma at an unusual site. Seven of 10 cases of osteosarcoma in WS occurred in the ankle or foot (Ishikawa, chapter 9). In 36 patients with osteosarcoma who did not have WS, there was only one at this site. The peculiarity of occurrence of this tumor in WS is heightened by the cluster of ALM at the same anatomic site.

Here there is an opportunity to search for an interaction between the WS gene (*WRN*) and a host factor or an environmental influence. Late in life the legs in WS patients are affected by muscle-wasting, loss of subcutaneous tissue, scleroderma, osteoporosis, ulcers, gangrene, and osteosclerosis of the toes (13). This effect can be seen in Goto's Fig. 2 (chapter 4), which shows 4 men with extremely thin legs, some with bandages. In 1980 Feibleman *et al.* (4) studied 42 patients at Roswell Park Cancer Center with melanoma of the foot, and found the frequency of ALM was greatest at weight-bearing sites. They suggested that there is a relationship between

the trauma of weight-bearing the risk of ALM. This effect may be accentuated in the vulnerable tissue of the legs in WS, and perhaps it contributes as well to the risk of osteosarcoma.

Might topical treatment of the cutaneous lesions of the legs interact with *WRN* (e.g., coal-tar preparations)? Another such interaction might involve mildly carcinogenic inhalants in patients with ALM of the nasal mucosa in a host made susceptible by *WRN*. Examples would be intranasal medication such as inhaled steroids for allergic rhinitis or calcitonin-salmon for osteoporosis.

In contrast to the relatively large number of ALM in Japanese with WS, only two non-Japanese with WS have developed melanoma (5). One had ALM (under a fingernail). ALM and thyroid carcinoma occur excessively in Japanese with WS, but not in Caucasians with the syndrome (Ishikawa, chapter 9). This difference may be due to dissimilar *WRN* mutations in the two races (Satoh *et al.*, chapter 3).

Diseases with High Risk of Meningioma

Among 147 neoplasms in Japanese with WS, 16 were meningiomas, one of which was malignant (5). Among 39 neoplasms in Caucasians with WS, 7 were benign meningiomas (5). Each group had one patient with multiple meningiomas. Meningiomas occurred with another neoplasm in 5 Japanese and 3 Caucasians. The other neoplasm was clinically diagnosed thyroid carcinoma in 3 Japanese and one Caucasian. Thus, about 2% in each series had this combination, which suggests a concordance not due to chance (a meningioma-thyroid carcinoma syndrome).

Meningiomas have been induced by radiation exposure (20), and occur excessively in several genetic disorders: neurofibromatosis-2 (16) and perhaps in Rubinstein-Taybi syndrome (12). Meningiomas have not been reported in the other two helicase-gene mutation syndromes (Monnat, chapter 10).

Osteosarcoma and Soft-Tissue Sarcoma

As shown in Table I, the syndromes with helicase disorders have dissimilar distributions by anatomic site of osteosarcoma (OS) and soft-tissue sarcomas (STS). OS is most common in Rothmund-Thomson syndrome (RTS) and almost absent in Bloom syndrome. Soft-tissue sarcoma is most common in the Li-Fraumeni syndrome (LFS) and there has been none in Bloom syndrome.

Congenital Malformations

No malformations are present at birth in WS. The earliest signs of the disease

TABLE I. Osteosarcoma Compared with Soft-tissue Sarcoma in Four Genetic Syndromes

Cancer	Percents of total cancers			
	Werner ^a	Bloom ^a	RTS ^a	LFS (15)
Osteosarcoma	6.3	2.0	43.0	14.5
Soft-tissue sarcoma	15.6	0	5.4	23.9

RTS, Rothmund-Thomson syndrome; LFS, Li-Fraumeni syndrome.

^a From Monnat, chapter 10.

are graying of the hair on average at 20 years and sclerosis of the skin at 26 years on average, which affect all patients (Goto, chapter 4). Bloom's syndrome exhibits dwarfism, a sun-sensitive rash of the face, and a high frequency of sister chromatid exchanges. RTS has poikiloderma and bone defects. There is no overlap in the clinical findings at birth of children with helicase gene mutations. Additional diseases beset patients with WS as they age, in contrast to other cancer-prone genetic syndromes that have anomalies at birth. Retinoblastoma has no birth defects related to the *RB-1* gene mutation. Li-Fraumeni syndrome, often linked to p53 mutation, has no birth defects or systemic disease, but has an excess of certain cancers under age 45 years (15) which overlap with those in WS (OS, soft-tissue sarcoma and non-lymphocytic leukemia), though not in the same proportion. The diversity of genetic malformation syndromes and of the cancers associated with them is mind-boggling. The pathogenesis of cancer in WS is discussed by Monnat in chapter 10.

Screening Children in WS Families

WS family members too young to have signs of the disease can be tested for the *WRN* mutation through ELISA, or for the *WRN* gene product by Western blotting. An assay for *WRN* protein function has recently been described by Prince *et al.* (18). A cohort of children who are found to be homozygotes can thus be studied for prodromal disease, and steps can be taken to slow its progress.

No Adolescent Growth Spurt

Goto (chapter 4) states that the first sign of WS is absence of an adolescent growth spurt, on average 15 years before other signs of WS make diagnosis possible. This is an intriguing finding. Ideally, WS should be in the differential diagnosis of this growth failure in areas of Japan with high rates of WS. These adolescents are too old to be seen by pediatricians. Endocrinologists would be most aware of WS, but it is unlikely that they would be consulted at this stage. In areas with high rates of WS, case ascertainment may be possible by review of school health records for failure to grow during the high school years. Testing for *WRN* mutations could then be done if deemed appropriate after careful examination and genetic counseling.

Disease Prevention in WS

If cohorts of patients can be identified early, evidence of complicating diseases may be detected, permitting earlier premorbid treatment. For example, the metabolic and end-organ damage associated with diabetes or hypercholesterolemia may be avoided or diminished. We can learn what percent of adults were *WRN* homozygotes but failed to meet the criteria for diagnosis, and if some patients with the gene mutation have no sign of the disease except for short stature. Can the disorders associated with *WRN* be lessened by modification of the diet, prompt treatment of diabetes mellitus, early cancer detection (e.g., thyroid cancer, usually curable by prompt treatment) and genetic counseling with reference to child-bearing? Are those with a *forme fruste* of the disease at increased risk of the neoplasia seen in patients

with the full complement of organ-systems affected? The question arises, is there a role for the chemoprevention of cancer?

Other Syndromes with Premature Aging

When “progeria syndromes” was entered into PubMed for a literature search, 147 references were listed — not only the syndromes described elsewhere in this monograph but also several others. Included are the 13th and 14th cases of Wiedemann-Rautenstrauch syndrome (WRS) (1, 22) first described in two sisters by Wiedemann and Snigula in 1977 with two more cases described by Wiedemann in 1979. This history is from Stoll *et al.* (22), whose case was a 10-year-old boy, who at birth had intrauterine growth retardation, two teeth, sparse hair, prominent scalp veins and wide anterior fontanelles. During infancy he developed a progeroid appearance, and at 3.5 years a marked deficiency of subcutaneous fat was noted. He had a triangular face, borderline mental deficiency, cholesterol levels in the upper range of normal and triglyceridemia.

The seventh case of Mulvihill-Smith syndrome was reported from Scotland in 1997 (2). The fullest description of the syndrome was published in 1975 (14). The first patient, a white male who at birth weighed 1.8 kg and whose length was 47 cm, had pigmented nevi on the trunk and neck. At age 11 years diabetes mellitus was diagnosed. The facial anomalies are shown in Fig. 1. At 17 years his skin was diffusely thin, taut and dry. Scalp hair was sparse and the upper trunk had scant subcutaneous tissue. Standard laboratory tests were normal. Fibroblast cell doublings done by George M. Martin were below normal for his age. Bone age was normal but height and weight were well below normal. Skin fibroblasts in culture

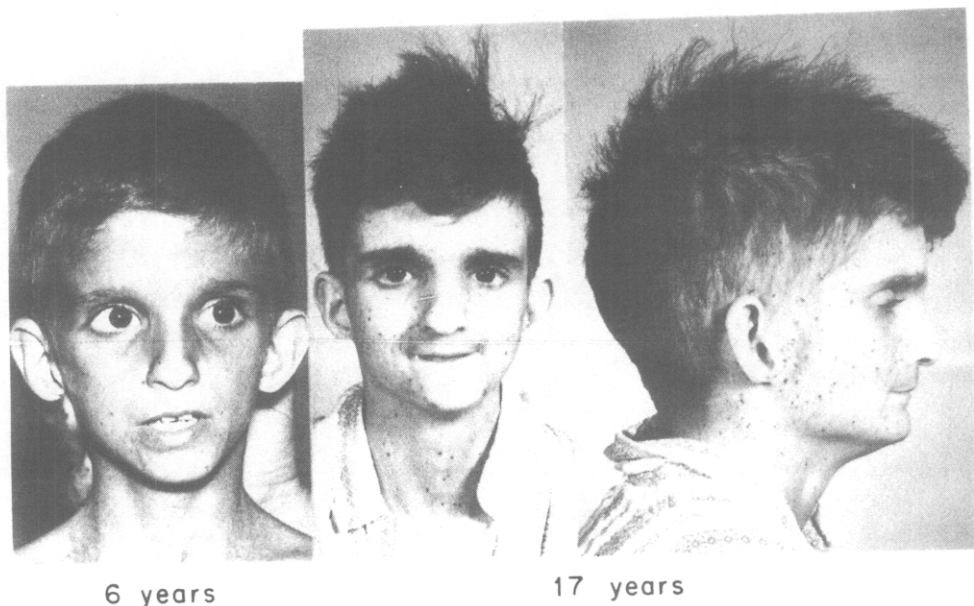


FIG. 1. Mulvihill-Smith syndrome: facial views at ages 6 and 17 years (14) (Provided by Dr. John J. Mulvihill, Oklahoma City Children's Hospital)

had the same increased number of doublings, 21, as were found in a healthy 17-year-old with diabetes. In Mulvihill-Smith syndrome there is no cytogenetic instability, important in predisposing to cancer (Monnat, chapter 10).

A report from Finland in 1997 (17) concerned what may be a newly recognized progeroid syndrome: a 10-year-old boy with delayed bone and dental maturation, pronounced acro-osteolysis, a very aged appearance and confluent skin lesions. His height and intelligence were normal. Another report from Finland in 1997 (8) concerned a newborn fatally ill with severe growth retardation, cataracts, lax skin, hypermobility of the joints, and insufficient production of procollagen types I and III. He shared signs of Ehlers-Danlos type IV syndrome, De Barsy syndrome and geroderma dysplastica. The clinical picture did not match that of previously known collagen disorders. This pair of cases from Finland suggests a greater awareness there than elsewhere of progeroid features in pediatrics, including features unlike those of previously described syndromes. Are pediatricians elsewhere overlooking features of progeria?

The Link between the Syndromes of Rothmund and Werner

Martin, in his history of WS, (chapter 1), noted that Werner thought the most similar previously described syndrome was that reported by Rothmund 36 years earlier, in 1868. The details were given in 1953 by Müller and Andersson (13). In 1996 Lindor *et al.* (7) of the Mayo Clinic noted that RTS had elements of aging. Then, when Furuichi's group sought a disease for a DNA helicase gene they had just identified (RECQL4), they collaborated with the Mayo group using its specimens from siblings with RTS and others from cell banks. In this way the disease and the gene were linked (6).

It used to be said that to know syphilis is to know medicine. Now, because of its immense diversity of manifestations, the same can be said of Werner syndrome.

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